



# Going retro: Transposable elements, embryonic stem cells, and the mammalian placenta

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# **Going retro: transposable elements, embryonic stem cells, and the mammalian placenta**

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Chuong proposed that the trophoblast of early mammals evolved a hypomethylated epigenome that was a permissive environment for retroviral replication. As a consequence, retroviral sequences have been repeatedly coopted into gene regulatory networks of trophoblast in a process that has contributed to rapid lineage-specific innovation in mammalian placentas [1]. Related ideas have been advanced by others [2]. Embryonic stem cells (ESCs) are also hypomethylated and exhibit rapid divergence of regulatory networks mediated by retroelements [3]. These similarities between trophoblast and ESCs may be related to adaptations of retroviruses to early zygotic genome activation (ZGA) in mammals.

Retroviruses may have evolved to replicate in trophoblast because placentas were waystations for infectious transmission of exogenous viruses from mothers to offspring and of endogenous viruses from offspring to mothers [4]. ESCs are also expected to be a nexus for adaptive proliferation of retroelements. Early transposition is better than late transposition because it increases the number of descendant cells that carry a copy of each new insertion, especially insertions in the progenitors of future germ cells. Natural selection is therefore expected to favor retroelements that become active soon after ZGA (if not before).

Precocious ZGA in mammals can be conjectured to be an evolutionary response to intergenerational and intragenomic conflicts occasioned by postzygotic maternal provisioning of embryos. Opportunities for maternal–zygotic conflict are minimal in oviparous taxa because the amount of yolk is determined before

fertilization, and the embryonic genome should accede to maternal control of early development if this provides protection against transposable elements (TEs). However, mammalian embryos evolve to take more from mothers than mothers evolve to supply. As a corollary, conflicts between maternal and paternal alleles of embryos favors the evolution of imprinted gene expression and demethylation of the paternal pronucleus by maternal factors. Hypomethylation and early ZGA may have made mammalian germlines particularly vulnerable to accumulation of retroelements that require transcription, followed by reverse transcription, for their replication, whereas the absence of transcription during the critical early cleavage divisions in fish and frogs may have restricted opportunities for endogenous retroelements. This may explain why mammalian genomes are dominated by retroelements but the genomes of zebrafish and *Xenopus* are dominated by DNA transposons [5].

Recent suggestions that a *function* of TEs is to enhance evolvability by facilitating the rewiring of regulatory networks may be no more than simple restatements of the observation that regulatory networks have evolved but are dubious if intended as claims that TEs have been tolerated as *adaptations* to facilitate evolutionary change. Active TEs are indeed a source of mutation that scatters regulatory components throughout the genome, but many more insertions are likely to have been deleterious, and eliminated by natural selection, than were beneficial. 'Restrictive' host genes that suppressed transposition would have been favored relative to 'permissive' host genes that tolerated transposition because restrictive genes avoid the immediate costs of transposition, while their descendants benefit, via sexual recombination, from any favorable mutations generated by permissive. TEs and 'host' genes are joint occupants of a body, their constructed niche, with a common interest in the body's somatic survival and germline reproduction. Transposition, however, is maintained as an adaptation of TE lineages that must continually change location to preserve their ability to move under the use-it-or-lose-it principle [4].

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